

*Epidemiology of Intraocular Melanoma**

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Introduction

Intraocular malignant melanoma (IMM) is a relatively rare tumor, but it affects an estimated 2000 people in the United States yearly. It is the most common primary tumor of the eye in adults (Shields 1983). The incidence of IMM has been studied in descriptive studies of populations and in case reports of individuals and families. Because of the rarity of the disease, few analytic studies have been undertaken. We recently completed a case-control study of 509 IMM patients and equal number of patients with detached retinas seen by Dr. Jerry Shields at the Ocular Oncology Service of the Wills Eye Hospital in Philadelphia. We include preliminary findings from that study in this review.

Descriptive Epidemiology

Current intraocular melanoma incidence rates are 8 per million person-years in the U.S. (Cutler and Young 1975), 8 per million in Norway (Mork 1961), 7 per million in Denmark (Jensen 1963), 5 per million in Finland (Raivio 1977), and 5 per million in England (Swerdlow 1983). Intraocular melanoma incidence rates rise with increasing age and are much higher in whites than blacks; the rates for men and women appear to be fairly similar.

It seems likely that intraocular melanoma is caused by some of the same factors as cutaneous malignant melanoma, since the common cell of origin is the melanocyte and dark-skinned populations are at much lower risk of both tumors. For cutaneous melanoma, complexion and hair color are established risk factors. Eye color and hair color also appear to be related to risk of intraocular melanoma (Gallagher et al. 1985).

Approximately 10% of cutaneous melanomas are familial. Familial predisposition to intraocular melanoma has been suggested because of scattered reports of intraocular melanoma occurring in first-degree relatives of patients, and reports of cutaneous and intraocular melanoma occurring within the same individuals and families. No clear precursor lesion for intraocular melanoma has been identified, but various other medical conditions have also been associated with intraocular melanoma (nevus of Ota, neurofibromatosis, nevoid basal cell carcinoma syndrome, choroidal nevi). Several studies suggest that

* *Abbreviation: IMM, Intraocular malignant melanoma*

hormone levels may affect cutaneous melanoma susceptibility, but little is known about intraocular melanoma. Ultraviolet radiation, the major environmental risk factor for cutaneous melanoma, may play a role in intraocular melanoma. Sunlight exposure was a risk factor in our recent study, but incidence rates within the U.S. and Finland are not related to latitude. Other environmental exposures have been suggested as possible causes of intraocular melanoma, including polychlorinated biphenyls, hydrazine, and dimethyl-sulfate.

Host Factors

Age is a strong determinant of intraocular melanoma risk, with current U.S. incidence rates rising from 0.1 per 100 000 person-years at age 20 to 3.7 per 100 000 person-years at age 85 (Young et al. 1981). As noted, differences in risk between men and women appear to be slight. In Finnish and American population-based studies, the incidence was slightly higher in women than men at ages below the mid-forties and slightly higher at older ages. In Danish and Norwegian population-based studies, the incidence was greater in men than in women for all ages (Jensen 1963; Mork 1961).

Race is strongly related to intraocular melanoma risk (Hakulinen et al. 1978). Scotto et al. (1976) estimated that the risk among whites was eight times greater than among blacks in the U.S. Although cutaneous melanoma is clearly associated with complexion and hair color (Elwood et al. 1984; Holman et al. 1983), this pattern has not yet been confirmed for ocular melanoma. Jensen found 69% of the normal Danish population had fair hair, while 61% of ocular melanoma patients had fair hair. There was a greater difference in color of the irides, with 61% of the normal population having fair irides (defined as blue, bluish-gray, grayish-blue, gray and greenish-gray) and 82% of the ocular melanoma patients having fair irides, with an estimated relative risk of 2.9 for people with fair irides (Jensen 1963).

Eye color, but not skin or hair color, was related to intraocular melanoma in our study. Blue-eyed subjects had the highest risk of melanoma, with an estimated relative risk of 1.7 compared with subjects with brown eyes. Unadjusted analysis showed that the patients were more likely to have fair skin, blonde or brown hair, and eastern European origin. When the analysis was adjusted for eye color, however, these differences disappeared. Conversely, adjusting for these variables did not change the risks for eye color. It is quite possible that reported eye color was a better index of actual skin color than the subject's report of skin color.

Genetic predisposition may be a factor in the development of intraocular as well as cutaneous melanoma, since there have been scattered reports of intraocular melanoma in first-degree relatives (Bowen et al. 1964; Green et al. 1978; Lynch et al. 1968; Silcock 1892; Tasman 1970). In our study, however, only 4 of 3422 (0.1%) first-degree relatives of patients had eye cancers, suggesting that familial occurrence probably accounts for very little of the disease. Unlike cutaneous melanomas, which are frequently multiple, bilateral intraocular melanomas are quite rare. It has been estimated that one case of bilateral choroidal melanoma occurs every 18 years in the U.S. (Shammas and Watze 1977).

Intraocular melanoma has been reported as a double primary with cutaneous melanoma (Paton and Thomas 1959), with ovarian cancer (Mullaney et al. 1984), and with breast cancer (Harvey and Brinton 1985). In our study, although the numbers are small and did not reach statistical significance, there is a two-fold risk of intraocular melanoma after ovarian tumors. There was no increased risk after breast cancer.

Nevus of Ota (oculodermal melanocytosis) is a recognized risk factor for both intraocular melanoma (Font et al. 1967; Halasa 1970) and cutaneous melanoma, but this risk has been difficult to quantitate. Intraocular melanoma has also been reported as part of the constellations of tumors which occur in neurofibromatosis (Gartner 1940), an autosomal dominant phakomatosis, and in nevoid basal cell carcinoma syndrome (Kedem et al. 1970), an autosomal dominant mesodermal abnormality.

Iris nevi may be related to development of intraocular melanoma, but in one study equal numbers of iris nevi were found in the eye that developed intraocular melanoma and the unaffected eye (Michelson and Shields 1977). Posterior choroidal nevi have also been thought to be precursor lesions, but Ganley and Comstock estimated that if intraocular melanoma arose only from choroidal nevi, the average annual incidence of intraocular melanoma would be 21 per 100 000 persons with choroidal nevi (Ganley and Comstock 1973). In our study, subjects with iris melanoma were approximately three times as likely as controls to have iris nevi, but not choroidal nevi. The nevi which were recorded in the medical records were separate from the tumor itself. Conversely, we found no significant association between choroidal nevi and choroidal melanoma. This may be because iris nevi are multiple more often than are choroidal nevi, and if a person has a single precursor lesion, it may in fact be the nevus that becomes a melanoma. Alternatively, there may be no association between choroidal nevi and choroidal melanoma.

Recently, a precursor lesion for cutaneous melanoma, the dysplastic nevus, has been characterized (Clark et al. 1978, 1984; Greene et al. 1985). These lesions identify individuals who are at high risk for both familial and sporadic melanoma. Two kindreds with cutaneous melanoma, intraocular melanoma, and dysplastic nevus syndrome have been described, but in these families the associations of cutaneous melanoma, dysplastic nevi, and intraocular melanoma appeared to be coincidental (Greene et al. 1983). A subsequent evaluation of a small series of intraocular melanoma patients revealed that intraocular melanoma patients had a 4.5% prevalence of dysplastic nevi, as against a 41% prevalence of dysplastic nevi in patients with sporadic cutaneous melanoma (Taylor et al. 1984). In our study, subjects were asked specifically about certain skin conditions possibly associated with intraocular melanoma, including skin melanoma, moles, other skin cancers, birthmarks such as the nevus of Ota, congenital nevi, café-au-lait spots, or other skin conditions such as psoriasis.

Patients with intraocular melanoma were twice as likely as controls to report prominent moles. At this point, we do not know whether these are true nevi, actinic keratoses, or other pigmented lesions. The numbers were very small, and the risks did not reach statistical significance, but cutaneous melanoma was slightly more common (relative risk = 1.6) in the intraocular melanoma cases. There was no difference in birthmarks or pigmentary abnormalities. In our study, cases were four times as likely as controls to have psoriasis. This statistically significant excess was not due to treatment with psoralens and ultraviolet radiation and persisted even in those who did not have this therapy.

The observation that we found no association with birthmarks or pigmentary abnormalities may be explained by the difference in data between case reports or clinical series, and questionnaire data. The data from clinical observation are much more accurate and precise than data obtained from a questionnaire. Even if there is a very high risk associated with the nevus of Ota, ocular melanocytosis, neurofibromatosis, or any other condition, it may not be found in a case-control study, simply because of reporting. Similarly, as noted above, "moles" according to the general population may be actinic keratoses, pigmented basal cell carcinomas, true nevi, hemangiomas, etc.

Environmental Factors

Ultraviolet radiation from sun exposure, the major environmental risk factor for cutaneous melanoma, has not been thought to be strongly related to intraocular melanoma risk, since it does not show the strong association with latitude characteristics of cutaneous melanoma (Lee 1982). For example, no latitude differences for intraocular melanoma have been found in the United States (Scotto et al. 1976) or Finland (Raivio 1977), or in a comparison of multiple countries (Hakulinen et al. 1978). It should be noted, however, that an examination of the effect of latitude in the United States is somewhat confused by the association of ethnicity and hence coloring with latitude (Morin et al. 1984). In the United States, tumor registries in the north include more fair-skinned, blue-eyed populations than the southern registries do. In addition, although the incidence of cutaneous melanoma is increasing rapidly, which has been attributed to increasing sun exposure (Lee 1982), the incidence rates of intraocular melanoma have remained stable over time (Scotto et al. 1976; Strickland and Lee 1981; Swerdlow 1983).

Previous U.S. studies have shown a difference in laterality by sex with an increase in left eye melanoma in men and right eye melanoma in women (Keller 1973; Scotto et al. 1976). It was hypothesized that this might relate to driving habits in the U.S., with the left eye being exposed to more sun and/or pollutants in males, and the right in females (Scotto et al. 1976). In our study, there was no difference in laterality in either sex.

Our study findings suggest that sunlight exposure does increase IMM risk, judging by differences between cases and controls in birthplace, freckling, sunbathing, sunlamp use, and eye protection (Tucker et al. 1985). Patients were three times more likely to be born in the southern states than controls, after adjustment for eye color, age, and sex. To exclude the possibility that referral bias accounted for the excess of cases born in the south, we looked at those study subjects living in greater Philadelphia at the time of diagnosis and found the same increased risk. Living in the south for a long time was less important than being born in the south as a predictor of melanoma risk. This is consistent with the observation that the lens filters most ultraviolet radiation by the adult years (Zigman 1983). Only a small number of study subjects had lived in the tropics and subtropics for 5 years or more, but they, too, showed a striking elevation in risk ($RR = 4$) (Tucker et al. 1985).

Freckles are an index of both sensitivity and exposure to sun. The cases were slightly more likely to have over 25 freckles ($RR = 1.4$). They were also more likely to use sunlamps ($RR = 1.4$), with some evidence of increasing risk with increasing frequency of use ($P = 0.10$). This relationship was not confounded by the effect of psoriasis. Study subjects with intraocular melanoma were more likely to sunbathe ($RR = 1.4$), but frequency of sunbathing did not appear to be related to risk (Tucker et al. 1985).

Eye protection was also associated with lowered intraocular melanoma risk in our study. Compared with subjects who almost always used eye protection when in the sun, those who did not had a 60% increase in risk (95% $CI = 1.0-2.2$), but there was no gradation in risk depending on whether the subjects wore protection occasionally, rarely, or never. Another form of eye shading that might protect against intraocular melanoma is corrective lens use. More patients with detached retina wore glasses most of the time than did patients with intraocular melanoma (64% vs 52%) (Tucker et al. 1985). Because of the poorer visual acuity of the patients with detached retina, we used a second control group with visual acuity similar to the cases and found a 20% reduction in risk, which was not statistically significant.

Not all indicators of sunlight exposure were related to intraocular melanoma risk in our study. For example, there was no difference in the total amount of leisure time that pat-

ients and controls spent outdoors, but there were differences in the types of outdoor leisure. Gardening as a hobby was associated with an increased risk of ocular melanoma ($RR = 1.6$), which was not attributable to fertilizer, pesticide, or herbicide use. Cases were also more likely to spend increased amounts of time out in the sun during vacations compared to everyday living ($RR = 1.3$). Adjusting for the length of vacation did not change the estimated risks (Tucker et al. 1985).

Social class was examined in a Finnish study as a rough occupational index, but the distribution of intraocular melanoma by social class was identical to the general population (Raivio 1977). In Denmark, there was a similar distribution of occupations in the case group and the general population, except for an increased percentage in domestic work and, possibly, construction work. The increased percentage of domestic workers was attributed to differences in employment reporting among housewives between the study questionnaire and population census questionnaire (Jensen 1963). In our study, the distribution of occupations was very similar among cases and controls. Time spent working outdoors also was similar among cases and controls. We examined the occupations with high ultraviolet exposure, such as welding, construction work, or farming, in which risk of intraocular melanoma might be elevated. Welders and construction workers had elevated risks according to these data, but farmers did not. Subjects who said they worked under bare fluorescent lights were at slightly increased risk. None of these estimates of occupation-specific relative risk was stable, because of the small numbers of workers in each category.

Exogenous estrogen may be a factor for cutaneous melanoma (Beral et al. 1977; Danforth et al. 1982; Helmrigh et al. 1983; Holly et al. 1983), but the issue is controversial. In this study, there was no difference in duration of use or type of oral contraceptives between cases and controls. Ever having been pregnant was associated with an increased risk of melanoma ($RR = 1.4$), but there was no increasing risk with increasing parity. There was also no effect of age at first pregnancy or latency between last pregnancy and diagnosis. The age at menarche and age at menopause were similar in the two groups. Postmenopausal estrogen use was associated with a significantly increased risk of melanoma, with dose response reaching a threefold risk in those who took postmenopausal estrogens for 6 years or longer.

Chemical exposures have been implicated in the etiology of both cutaneous and intraocular melanoma. Cutaneous melanoma has been associated with exposure to polychlorinated biphenyls and other industrial toxins (Bahn et al. 1976). Intraocular melanoma has occurred in excess in chemical plant workers in West Virginia, possibly due to hydrazine and dimethylsulfate exposure (Albert et al. 1980). Our preliminary analysis suggests an increased risk associated with working in the plastics industry or with the manufacture of plastics. Patients were more likely to be exposed to chemicals and radiation, as well as pesticides, fertilizers, and paints. There were no significant effects of either alcohol or tobacco use.

Future studies need to confirm and further refine these results, particularly to clarify the mode and intensity of ultraviolet exposure, and the effects of early life and intermittent ultraviolet exposure on the risks of IMM. In this way, it should be possible to lower the incidence of ocular melanoma, which is presently a serious cause of morbidity and vision loss.

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